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## **Long-term neurodevelopmental outcome with hypoxic-ischemic encephalopathy**

Perez, Anna ; Ritter, Susanne ; Brotschi, Barbara ; Werner, Helen ; Caffisch, Jon ; Martin, Ernst ; Latal, Beatrice

**Abstract:** **OBJECTIVES:** To determine the long-term neurodevelopmental outcome for children after hypoxic-ischemic encephalopathy (HIE) without major disability, and to examine neonatal injury patterns detected on cerebral magnetic resonance imaging (MRI) in relation to later deficits. **STUDY DESIGN:** Prospectively enrolled children with HIE and neonatal cerebral MRI data ( $n = 68$ ) were examined at a mean age of 11.2 years (range, 8.2-15.7 years). Eleven children had a major disability (ie, cerebral palsy or mental retardation). Brain injury was scored according to the region and extent of injury. **RESULTS:** Children without major disability ( $n = 57$ ) had lower full-scale and performance IQ scores compared with norms ( $P = .02$  and  $.01$ , respectively), and the proportion of children with an IQ  $< 85$  was higher than expected ( $P = .04$ ). Motor performance on the Zurich Neuromotor Assessment was affected in the pure motor, adaptive fine motor, and gross motor domains, as well as in the movement quality domain (all  $P < .001$ ). Watershed injury pattern on neonatal MRI correlated with full-scale and verbal IQ scores ( $P = .006$  and  $< .001$ , respectively), but neonatal MRI pattern did not correlate with motor performance in children without major disability. **CONCLUSION:** Children who sustained neonatal HIE without major disability are at increased risk for long-term intellectual, verbal, and motor deficits. The severity of watershed injury is correlated with later intellectual performance. Long-term follow-up examinations are necessary for early detection of neurodevelopmental impairment and early initiation of adequate therapies.

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**Title:** Long-term neurodevelopmental outcome in children with hypoxic-ischemic encephalopathy: the role of neonatal MRI

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**Abstract**

**Objectives:** To determine the long-term neurodevelopmental outcome for children after hypoxic-ischemic encephalopathy without major disability and to examine the role of neonatal cerebral MRI injury patterns in relation to later deficits.

**Study design:** Sixty-eight prospectively enrolled children with hypoxic-ischemic encephalopathy and neonatal cerebral MRI were examined at a mean age of 11.2 years (range 8.2 – 15.7 years). Eleven children had a major disability (cerebral palsy or mental retardation). Brain injury was scored according to region and extent of injury.

**Results:** Children without major disability (n=57) had lower total and performance IQ scores compared to the norm ( $p=0.02$  and  $0.01$ , respectively) and the proportion of children with an IQ  $< 85$  was higher than that expected ( $p= 0.04$ ). Motor performance on the Zurich Neuromotor Assessment was affected in the domains 'pure motor', 'adaptive fine' and 'gross motor' as well as in the domain 'movement quality' (all  $p$ -values $< 0.001$ ). Watershed injury pattern on neonatal MRI correlated with total and verbal IQ ( $p=0.006$  and  $< 0.001$ , respectively), while neonatal MRI pattern did not correlated with motor performance in children without major disability.

**Conclusions:** Children after neonatal hypoxic-ischemic encephalopathy without major disability are at higher risk for long-term intellectual, verbal and motor deficits. Severity of watershed injury correlates with later intellectual performance. Long-term follow-up examinations are necessary for early detection of neurodevelopmental impairments and early initiation of adequate therapies.

## Introduction

Hypoxic-ischemic encephalopathy (HIE) occurs in 1-6 of 1000 live term births and is a major cause of neurodevelopmental disability.(1, 2) Long-term neurodevelopmental outcome depends on the severity of HIE,(2) with adverse outcomes being rare in children with mild HIE, more common in children with moderate HIE and invariably present in children with severe HIE.(3) Many outcome studies of children with HIE focus on major adverse outcomes such as death, cerebral palsy (CP) or severe cognitive impairment. However, deficits in the absence of CP or major disability may include intellectual impairments, specific memory and verbal problems, difficulties in executive functions, behavior, and social competence(4, 5) and some studies have also reported motor problems in children with only mild HIE.(6, 7) It is not clear whether these problems persist into adolescence and young adulthood. Some studies including neonates with biochemical markers of hypoxia showed that problems with short-time memory and time perception, as well as difficulties in social interaction persisted into young adulthood.(8, 9) Neonatal cerebral MRI has become the standard tool to determine the timing of brain injury and to define injury patterns.(10) It has been widely accepted that the risk of an abnormal neurodevelopmental outcome increases with the severity of brain injury.(11, 12) However, the pattern of injury may be even more predictive than the severity of lesions shown on MRI. The basalganglia/thalamus pattern has been associated with severely impaired motor and cognitive outcomes (2, 7) and the watershed-predominant pattern with cognitive impairments that often occur in the absence of functional motor deficits.(2, 3) More recently, a correlation of watershed-predominant pattern of injury with verbal IQ has been demonstrated for children at the age of four years.(13) Little is known on the association between neonatal MRI injury pattern and long-term neurodevelopmental outcome in children without major disability. Therefore, our study aimed to determine the spectrum and severity of neurodevelopmental impairments in 11 year old non-disabled survivors of HIE and to determine the role of MRI patterns of injury on neurodevelopmental outcomes.

## Methods

Between 1989 and 1993, 94 term neonates, born at 36 or more completed weeks of gestation, who were at risk for hypoxic-ischemic brain injury due to perinatal asphyxia were included into this prospective cohort study. The study was approved by the local ethics committee and informed consent was obtained from the parents. For enrollment into the study, three groups of diagnostic criteria were established (Table 1); at least one criteria in two groups had to be fulfilled. Infants with a genetic syndrome or major malformations, a metabolic and/or endocrinological disease, requiring surgery, cardiovascular reanimation (attributable to a condition other than asphyxia), exchange transfusion due to severe hyperbilirubinemia during the neonatal period, repetitive hypoglycemia  $< 1$  mmol/l, meningitis and/or encephalitis or septic shock were excluded from the study.

The severity of HIE was clinically assessed using the Sarnat score during the first days of life.<sup>(11)</sup> Of 94 infants, 68 were eligible for follow-up examination at 10 years of age (see supplemental figure “study group algorithm”). Of 68 eligible children, complete neurodevelopmental assessment could be obtained in 57 (84%). Of the remaining 11 children (16%), nine had a severe CP (Palisano grade 4 or 5) and two had a mild CP (Palisano 1) with severe mental retardation (IQ $<55$ ). These 11 children were grouped into the category ‘major disability’. Outcome information for the 11 children with major disability was obtained by parental telephone interviews in nine and two children were examined at the Child Development Center Zurich. Informed consent was obtained from the parents.

The ethics committee of the University Children's Hospital Zurich and the Canton Zurich confirmed that the study was performed according to the Declaration of Helsinki, and conformed to legal and ethical norms.

### *Neuroimaging*

Cerebral MRI was performed in all infants between day one and day 30 of life, 56 of 68 eligible infants (82.4%) had the MRI scan performed within the first week of life, 4 infants (6%) had the scan performed on day one. Three of those four infants in whom MRI was performed on day 1 and who were eligible for follow-up had a repeat MRI at six days, one and three months, respectively. Sixty-three (86.8%) had the MRI scan performed within the first ten days of life. Axial T1-weighted images (T1WI; TR 500ms, TE 30 ms) and T2-weighted images (T2WI; TR 3000 ms, TE120ms) were obtained using a 256x256 imaging matrix, on a 2.35 T 40-cm bore system. When parasagittal lesions in very cephalad regions were suspected on axial MRI, additional coronal images were performed.(14) A neuroradiologist (E.M.), blinded to the participants' clinical condition and neurodevelopmental outcomes, scored each neonatal MRI on 3 scales, rating degree of injury from 0-3 (normal-severe injury) for three injury patterns: watershed, basal ganglia/ thalamus and perirolandic region, using the scoring system described in previous publications.(14, 15) Basically, each region is graded according to degree of HIE injury severity, 0 being no injury, 1 mild, 2 moderate and 3 severe injury in that specific injury site. Patterns of injury on MRI were then defined on the basis of the predominant site of injury: watershed predominant, basal ganglia/thalamus predominant, perirolandic region predominant and normal (see Table 3).

### *Neurodevelopmental outcome*

Children were examined at the Child Development Center of the University Children's Hospital of Zurich by one experienced developmental pediatrician (S.R), who was aware of the clinical course. Socioeconomic status was estimated on a 12-point scale based on paternal occupation and maternal education (each a score 1-6, total score 2-12).(16) Children were examined with the German version of the Wechsler Intelligence Scale for Children-Revised (WISC-R).(17) This

test consists of a Verbal IQ and a Performance IQ, which together form the Full Scale IQ. In two children, the German version of the Kaufman-Assessment Battery for Children (18) was administered because they were not able to complete the WISC-R.

### *Neuromotor Assessment*

Cerebral palsy was classified according to the European guidelines(19) and severity graded according to Palisano et al.(20) Motor performance was assessed with the Zurich Neuromotor Assessment (ZNA). The ZNA is a standardized testing procedure for children aged 5 to 18 years, in which distinct motor tasks are assessed for timed performance and movement quality with age- and gender- specific normative data.(21, 22) The testing procedure includes the assessment of pure motor tasks, adaptive fine motor tasks, adaptive gross motor tasks, static balance and stressgaits. The child's performance is videotaped. Movement quality is scored from videotape recordings by classifying frequency (score 0-10) and degree (score 0-3) of contralateral associated movements during timed performance and stressgaits. One trained research assistant (H.W.) rated associated movements from video recordings. Inter-rater reliability was assessed for 20 children with an experienced instructor who was involved in the development of the ZNA (J.C.). Kappa coefficient was 0.82. The results of the ZNA are expressed as components: pure motor, adaptive fine and gross, static balance component and associated movement component. Performance in the ZNA is expressed as standard deviation from the mean of the reference population (Z score) according to age and sex. A negative Z score reflects performance below average (slow timed performance, frequent and strong associated movements), a positive Z score performance above average (fast timed performance or few and weak associated movements). Outcome was dichotomized at the 10<sup>th</sup> percentile to express poor (<10<sup>th</sup> percentile) outcome.

### *Statistical analysis*

Analyses were performed with SPSS for Windows (SPSS 18.0, SPSS Incl., Chicago, IL). Differences between patients and norm values were calculated using the Wilcoxon paired rank-sum test, differences between subgroups using the Mann-Whitney U test for nonparametric data, the chi square test and the Fisher's exact test for categorical variables. Correlation analyses were performed using Spearman Rank coefficient, as variables were non-normally distributed. Multiple linear regression analysis was performed to evaluate the independent association of MRI abnormalities and other neonatal and outcome variables on total IQ within the group of children without major disability. Neonatal variables were included if they were either correlated ( $p=0.10$ ) with one outcome variable (SES with IQ, head circumference with IQ and with pure motor outcome, birth weight with IQ) or they were included based on the assumption that they may be associated with the outcome based on previous publications (gender, CP). A p-value of less than 0.05 was considered statistically significant.

### **Results**

Study participants ( $n=68$ ) did not differ significantly from children lost to follow-up in their clinical baseline data (supplemental Table). Cerebral palsy was assessed at the 10-year follow-up examination for the participants and at previous examinations for the non-participants (information available for 12 non-participant children). There was no difference in CP prevalence between participants and non-participants (22/68 (32.4%) versus 3/12 (25%);  $p=0.74$ ).

Eleven children had a major disability (nine severe CP and two mild CP and severe mental retardation). The comparison of baseline clinical characteristics showed that children with major disability had higher Sarnat scores (Table 2). On neonatal MRI, children with major disabilities had higher injury scores on all scales than children without major disabilities (Table 3).



The 57 children without major disability were examined at a median age of 11.2 years (range 8.2 – 15.7 years). Outcome is presented in Table 4. Eleven children (19.3%) were diagnosed with mild CP (ten with Palisano grade 1 and one with Palisano grade 2). Two children (one with CP, one without CP) were diagnosed with epilepsy. Mean performance, verbal and total IQ for the non-disabled children were within the normal range, but total and performance IQ were significantly lower compared to the population norm. While the proportion of children with an IQ < 85 (-1 SD) was higher than expected (expected proportion 15.9%), the proportion of children with an IQ < 70 (- 2 SD) was not (expected proportion 2.3%).

Motor testing was performed in 53 of the 57 children without major disability. Of the four children who could not be tested, two had a mild CP. Mean motor performance in the ZNA was below the expected norm of 0 in all components except the static balance (mean pure motor -1.37,  $p<0.001$ ; adaptive fine motor component -1.10,  $p=0.004$ ; adaptive gross motor -1.0,  $p=0.02$ ; static balance 0.38  $p=0.01$ ; associated movements -1.31,  $p<0.001$ ). Further, the proportion of children performing below the 10th percentile was significantly higher in all components except the static balance compared to the expected 10% in the normative sample (Table 4). When children with mild CP were excluded, motor performance remained poorer than the norm in the motor domains pure motor ( $p<0.001$ ), adaptive fine motor ( $p=0.02$ ) and associated movements ( $p<0.001$ ). The proportion of children without CP performing below the 10<sup>th</sup> percentile remained higher in all components (all  $p<0.001$ ) except the static balance.

Within the group of children without major disability ( $n=57$ ), those with CP who could perform the motor testing ( $n=8$ ), performed poorer on all motor components compared to those without CP ( $n=45$ ; pure motor  $p=0.003$ , fine motor  $p=0.002$ , gross motor  $p<0.001$ , static balance  $p=0.05$ , associated movements  $p=0.04$ ). The same was true for the performance IQ and the total IQ (both  $p=0.001$ ), but not for the verbal IQ ( $p=0.23$ ).

Within the group of children without major disability, the correlation analysis revealed that increasing severity of watershed injury, i.e. higher injury score was significantly associated with

lower total IQ scores and lower verbal IQ scores (correlation coefficient -0.32;  $p=0.006$  and -0.48;  $p<0.001$ , respectively; Figures 1a, b). No association was seen between the other two injury pattern scores with verbal or performance IQ scores (basal ganglia/thalamus  $p$ -values: 0.98 and 0.51, respectively; perirolandic region  $p$ -values: 0.96 and 0.29, respectively). None of the injury pattern scores on MRI correlated with motor performance. There was a weak correlation between higher watershed injury score and poorer fine motor performance ( $R = -1.92$ ,  $p=0.17$ ). In the multiple linear regression analysis (including the variables socioeconomic status, head circumference at birth, gender, watershed injury score and CP at the time of examination), the watershed injury score was independently associated with poorer total IQ (4.9 IQ score decrease per injury WS injury score;  $p=0.01$ ). Both, lower head circumference at birth and CP at the time of examination were also independently associated with lower total IQ (3.2 IQ score decrease per 1 cm decrease of head circumference;  $p=0.003$ ; and 9.7 IQ score decrease in the presence of CP;  $p=0.03$  respectively).

When all 68 children, including also those with major disability, were analyzed, there was a significant correlation between all MRI injury pattern scores and major disability (severe CP or severe mental retardation). Basal ganglia/thalamus scores and perirolandic region scores showed the strongest correlation (Spearman correlation  $R=0.52$   $p<0.001$  and  $R=0.60$ ,  $p<0.001$  respectively). Watershed scores were also significantly associated with adverse neurodevelopmental outcome, ( $R=0.37$   $p=0.002$ ). If the analysis included only those children who had an MRI scan within the first week of life,  $p$ -values all remained statistically significant or were even more significant than if all children were included into the analysis.

## Discussion

In this study we investigated the association between neonatal brain injury and neurodevelopmental outcomes in children after HIE without major disability. We found that children without major disability were at increased risk for intellectual and motor deficits. Watershed injury on cerebral MRI predicted poorer intellectual, in particular verbal, outcome. Motor outcome in children without major disabilities was not related to any of the other cerebral injury patterns. However, when children with major disability (severe CP or severe mental retardation) were included, more severe injury in the basal ganglia/thalamus and perirolandic region was strongly related to adverse outcome.

We confirmed that children with HIE suffer from long-term neurodevelopmental impairments, also in the absence of major disability. Impairments were found in overall intellectual functioning, with total IQ's ranging in the low-normal range. Performance IQ was particularly affected and the proportion of non-disabled children with an IQ < 85 was higher than expected, corresponding to a higher rate of learning disabilities. Further, in the absence of CP, the majority of motor domains were affected with up to a three times higher rate of poor performance. Our findings are in line with previous studies demonstrating that the outcome after HIE is not limited to CP and/or severe cognitive impairment, but can be associated with cognitive deficits (3, 4, 23) as well as with impaired motor skills in the absence of CP.(3, 7, 24) Robertson et al. were the first to examine school-age neurodevelopmental outcome in children after HIE. They found that non-disabled survivors after moderate HIE showed marked delays in reading, spelling and arithmetic and were more likely to be at least one grade behind controls or those with mild HIE. The severity of HIE was based on clinical parameters and neonatal neuroimaging was not performed.(25) In the study by Marlow et al. children with moderate HIE showed deficits in language and sensorimotor domains as well as in narrative memory and sentence repetition. They were more likely to require extra educational assessment, teaching provision and support, even though they had no overt neuromotor impairments.(26) In addition to a global effect on

intelligence, HIE can also lead to specific deficits such as memory dysfunction, learning deficits (5) and impaired language skills.(27) Importantly, poorer verbal IQ at four years of age was related to the severity of watershed-distribution brain injury in a prospective study by Steinman et al.(13) Our findings are in line with these results and demonstrate that the effect of watershed brain injury on verbal abilities persists in older, school-aged children. Interestingly, and similar to our findings, Steinman et al. did not find an association between the degree of basal ganglia/thalamus injury and verbal or non-verbal cognitive outcome. This finding appears contradictory to several studies describing the worst neurodevelopmental outcomes for children with basal ganglia/thalamus injuries on neonatal MRI.(7) However, in the analysis of Steinman et al. only children with no functional motor impairment were included. When all children was examined at 30 months, injury predominating in the basal ganglia/thalamus was associated with the worst cognitive and motor outcomes.(4) This is similarly true for our study: when the subgroup of children with major disability was included in the analysis, basal ganglia/thalamus injury scores and periorolandic region injury scores showed a significant correlation with adverse outcome. These findings suggest that the impact of basal ganglia/thalamus injury on neurodevelopmental outcome, although highly significant in severely affected children, might not be as relevant in children with HIE without major disability. This is in line with our findings that, despite poorer motor performance, none of the motor domains of the ZNA correlated with the basal ganglia score in children without major disabilities.

Children's motor performance scored significantly more often below the 10th percentile than in the normative population in all but the static balance component. This was also true when children with mild CP were excluded. A possible explanation for the exception of the static balance component might be that this component is not as discriminatory in the detection of subtle motor deficits as the other components. Similar observations with regard to poor motor performance in the absence of CP have also been reported by other authors. In a cohort study of 80 children after neonatal HIE, motor skills at nine years of age (assessed with the Movement

Assessment Battery for Children) in children without CP were impaired and correlated with moderate/severe findings in the neonatal and/or childhood MRI.(23) Barnett et al. reported that 15% of non-disabled children with HIE showed minor neurological dysfunction and/or perceptual-motor difficulties at the age of 5-6 years. These observations were largely reflected by neonatal MRI findings: 80% of the children with minor neurological dysfunction and/or perceptual-motor difficulties had mild or moderate basal ganglia or more marked white matter lesions.(7)

The clinical implications of our findings are, that children with HIE who have learning and motor difficulties, are likely to face school problems later in life. A study from Norway showed that children with clinical signs of HIE had a sevenfold increased risk of need for extra resources in kindergarten and a threefold increased risk of intervention at school with a below average performance in reading, writing, spelling and mathematics when surveyed at school age.(6) Therefore, children after HIE without major disability need long-term detailed follow-up examinations to detect neurodevelopmental problems that may cause school difficulties.

### Limitations

Our study has several limitations worth mentioning. Our study did not comprise a control group. However, we used standardized test batteries with normative reference values. Further, developmental assessment was not blinded. At the time of patient recruitment, magnetic resonance spectroscopy was not routinely used in patients with HIE. Magnetic resonance spectroscopy is especially helpful when a conventional MRI is performed on day one, when tissue changes are often restricted to cerebral edema.(28) Similarly, no advanced MRI technique such as diffusion-weighted imaging (DWI) was used and morphometric analyses were not performed. Today, imaging standards have changed and current recommendations include DWI and magnetic resonance spectroscopy.(28). Our cohort is rather old and the care of newborns with HIE has changed since. In particular, therapeutic hypothermia has been

introduced as a standard treatment. Further, neonatal aEEG was not assessed in our patient cohort at the time of enrollement. Nowadays, aEEG and other electrophysiological tools are neuromonitoring tools that are being applied in the NICU and that provide excellent prognostic value particularly in this patient population (29).

## Conclusion

In conclusion, our findings indicate that children with neonatal HIE who survive without major disabilities are at increased risk for long-term cognitive and/or neuromotor deficits. Neonatal MRI patterns of brain injury are associated with deficits in specific neurodevelopmental domains. In particular, the severity of watershed injury correlates with later intellectual performance in children without major disabilities. Mild to moderate cognitive and/or neuromotor deficits may be missed during follow-up examination at a younger age and may manifest only as children become older. Thus, careful long-term follow up examinations are mandatory in these children. This is particularly important for children who are currently treated with therapeutic hypothermia.

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### **List of abbreviations**

CP	Cerebral palsy
HIE	Hypoxic-ischemic encephalopathy
MRI	Magnetic Resonance Imaging
WISC-R	Wechsler Intelligence Scale for Children-Revised
ZNA	Zurich Neuromotor Assessment

**Figure legend**

Figure 1a and 1b: Box plots for total and verbal IQ scores in relation to watershed injury score in children without major disability. Horizontal line equals median, lower and upper border equals 25th and 75th percentile, whiskers represent the highest and lowest values that are not outliers or extreme values.